



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:  
Ralf BERTRAM  
3968.026

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Examiner: Zucker, Paul A

For: PROCESS FOR THE PREPARATION OF PHENYLENE-BIS-  
BENZIMIDAZOLE-TETRASULFONIC ACID DISODIUM SALT

DECLARATION UNDER 37 C.F.R. § 1.132

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Sir:

I, Dr. Oskar Koch, Symrise GmbH & Co. KG, Mühlenfeldstraße 1, 37603 Holzminden, Germany declare and state that I have spent the last 17 years involved in research and development related to fragrances and aroma chemicals.

I joined the company Symrise GmbH & Co. KG (formerly: Haarmann & Reimer GmbH) in 1986 after having obtained my Ph.D. in chemistry at the University of Hannover in Germany.

Since the beginning of my activities at Symrise GmbH & Co. KG I have been in charge of the research and development of fragrances and aroma chemicals. My activities as a chemist during the last 17 years are characterized by several highlights, and for some of these highlights Symrise GmbH & Co. KG decided to apply for both national and international patents, in the field of the present invention for example US 5,965,066; US 6,042,814; US 6,153,175; US 6,258,963; WO 02/38537.

I am familiar with the prosecution history of the above-identified application, including the Office Action dated June 17, 2003. I note the Examiner's position in the June 17<sup>th</sup> Office Action, i.e. that there was allegedly no evidence on record that (1) would lead one of ordinary skill in the art to expect an increase in impurities with extended reaction times, and (2) would permit the Examiner to assess any differences in outcome between the prior art process and the process of the invention (whether differences in degree or differences in kind).

The following experimentation was conducted by me or under my direct supervision, using the closest examples of the prior art, Pelzer (US Patent No. 5,585,091).

The following comparative experiments were conducted to demonstrate that:

- the method of the present invention produces a composition that is free of discoloring byproducts (see Attachment A, bottle on the right, showing a white color). In contrast, the method of the prior art produces a product that is colored (see Attachment A, bottle on the left, showing a pink color);

- the process of the present invention produces a composition that is free of discoloring byproducts despite the fact that the process actually increases the amount of trisulfonic impurities. Surprisingly, the process results in a decrease in discoloration. In contrast, the prior art only teaches reducing the amount of the trisulfonic acid impurity, but does not reduce discoloring byproducts;

- in this particular process, (1) an extension in reaction time or (2) an increase in reaction temperature results in an increase in discoloring impurities (due to an increase in side reactions, condensations, polymerizations, decompositions, or other subsequent reactions of the product, see HR 144-2);

-when the extended time and increased temperature of the present invention was used in conjunction with the process of the prior art, the process of the prior art did not lead to a colorless product; and

-when the process of the present invention was used in conjunction with the shorter reaction time of the prior art, the resulting product was still discolored.

#### EXPERIMENT

Five (5) different resulting phenylene-bis-benzimidazole-tetrasulfonic acid disodium salts (N.H. AP) were tested in the below cosmetic formulation, and their stability at two different temperatures (20°C and 40°C) with respect to discoloration was observed after 2 weeks and after 4 weeks.

#### Preparation procedure:

Step 1: Part A: All of the constituents were mixed together, except ZnO. Then, the ZnO was added. The resulting mixture was heated to 85°C.

Step 2: Part B: The constituents were mixed together, and the resulting mixture was heated to 85°C.

Step 3: Part B was added to Part A. After cooling to ambient temperature (approx. 25°C), the emulsion was homogenized by stirring (e.g., with an Ultra Turrax mixer).

Cosmetic testing formulation of W/O-emulsion for phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt (N.H. AP):

Table 1

	Dehymuls PGPH	Polyglyceryl-2 Dipropylhydroxystearate	3.00
	Monomuls 90-0-18	Glyceryl Oleate	1.00

	Permulin 2550	Beeswax (Cera Alba)	1.20
	Myritol 318	Caprylic/Capric Triglyceride	17.00
	Copherol 1250		0.50
	Zinkoxid neutral H&R	Zinc Oxide	5.00
B	Wasser, dest.	Water (Aqua)	41.80
	Phenonip	Phenoxyethanol (and) Methylparaben (and) Ethylparaben (and) Propylparaben (and) Butylparaben	0.50
	N.H. AP	N.H. AP employed as a 10% wt solution in water after neutralization with sodium hydroxide	30.00

The five different N.H. AP qualities prepared and incorporated into the cosmetic formulation above were:

HR 144: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1

HR 144-1: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1, the treatment with activated carbon being repeated one time

HR 144-2: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1, the reaction time and temperature corresponding to the present invention

HR 144-3: N.H. AP according to the present invention, the reaction time corresponding to Pelzer (US Patent No. 5,585,091), example 1

HR 285: N.H. AP according to the present invention

Table 2

after 2 weeks	HR 144	HR 144-1	HR 144-2	HR 144-3	HR 285
25°C	slightly pink	slightly pink	faintly pink	faintly pink	white
40°C	pink	pink	slightly pink	slightly pink	white

Table 3

after 4 weeks	HR 144	HR 144-1	HR 144-2	HR 144-3	HR 285
25°C	pink	pink	slightly pink	slightly pink	white
40°C	pink	pink	pink	pink	white

HR 144: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1

108 g of purified o-phenylenediamine was introduced into 500 g of sulfuric acid, 96%, and 800 g of chlorosulfonic acid was added dropwise over a period of 1.5 hours. The mixture was heated at 120°C for 15 minutes; HCl was continuously released, was cooled to 70°C and was treated with 83 g of terephthalic acid. The reaction mixture again released HCl and was heated to 180°C. After a reaction time of 30 minutes at 180°C, it was cooled to 80°C and poured onto 2,500 parts of ice.

The crystallize precipitate was filtered off, was introduced into 1,610 g of water at 50°C and was suspended (pH

2.4). Then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product. Then, 11 g of activated carbon was added; the mixture was heated to 55°C and after-stirred for 2 hours and filtered. Then, the filtrate was treated with concentrated (96% wt.) sulfuric acid. Then, the temperature was maintained at 50°C; the mixture was stirred for 2 hours under nitrogen and cooled to 25°C. The mixture was then filtered, and the filter cake was washed with 1,430 g of water, which produced the phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt, which was dried in vacuo.

The thus obtained phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt showed a content of phenylene-bis-benzimidazole-trisulfonic acid disodium salt of about 1.0% by weight. The residual moisture of about 1 - 2 % by weight was not taken into account.

HR 144-1: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1, the treatment with activated carbon being repeated one time

108 g of purified o-phenylenediamine was introduced into 500 g of sulfuric acid, 96% and 800 g of chlorosulfonic acid was added dropwise over a period of 1.5 hours. The mixture was heated at 120°C for 15 minutes, HCl was continuously released, cooled to 70°C and treated with 83 g of terephthalic acid. The reaction mixture again released HCl and was heated to 180 °C. After a reaction time of 30 minutes at 180°C, it was cooled to 80°C and poured onto 2,500 parts of ice.

The crystallizate precipitate was filtered off, was introduced into 1,610 g of water at 50°C and suspended (pH 2.4); then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product.

Then, 11 g of activated carbon was added; the mixture was heated to 55°C and after-stirred for 2 hours and filtered. The filtrate was treated with concentrated (96% wt.) sulfuric acid. Then, the temperature was maintained at 50°C; the mixture was stirred for 2 hours under nitrogen and cooled to 25°C; the mixture was then filtered, and the filter cake was then washed with 1,430 g of water, giving the moist phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt.

The moist phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt was introduced into 1,610 g of water at 50°C and suspended (pH 2.4). Then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product. Then, 11 g of activated carbon was added. The mixture was heated to 55°C and after-stirred for 2 hours and filtered. The filtrate was treated with concentrated (96% wt.) sulfuric acid. The temperature was maintained at 50°C. The mixture was stirred for 2 hours under nitrogen and cooled to 25°C; the mixture was then filtered. The filter cake was then washed with 1,430 g of water, giving the phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt, which was dried in vacuo.

The thus obtained phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt showed a content of phenylene-bis-benzimidazole-trisulfonic acid disodium salt of about 1.0% by weight. The residual moisture of about 1 - 2 % by weight was not taken into account.

**HR 144-2: N.H. AP according to Pelzer (US Patent No. 5,585,091), example 1, the reaction time and temperature corresponding to the present invention**

108 g of purified o-phenylenediamine were introduced into 500 g of sulfuric acid, 96% and 800 g of chlorosulfonic acid

was added dropwise over a period of 1.5 hours. The mixture was heated at 120°C for 15 minutes; HCl was continuously released. The mixture was cooled to 70°C and was treated with 83 g of terephthalic acid. The reaction mixture again released HCl and was heated to 110-120 °C. After a reaction time of 10 hours at 110-120°C, it was cooled to 80°C and poured onto 2,500 parts of ice.

The crystallizate precipitate was filtered off, was introduced into 1,610 g of water at 50°C and was suspended (pH 2.4). Then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product. Then, 11 g of activated carbon was added, the mixture was heated to 55°C and after-stirred for 2 hours and filtered. The filtrate was treated with concentrated (96% wt.) sulfuric acid; then, the temperature was maintained at 50°C. The mixture was stirred for 2 hours under nitrogen and cooled to 25°C. The mixture was then filtered and the filter cake was then washed with 1,430 g of water, giving the phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt, which was dried in vacuo.

The thus obtained phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt showed a content of phenylene-bis-benzimidazole-trisulfonic acid disodium salt of about 1.8% by weight. The residual moisture of about 1 - 2 % by weight was not taken into account.

**HR 144-3: N.H. AP according to the example of the present invention, the reaction time corresponding to Pelzer (US Patent No. 5,585,091), example 1**

609 g of sulfuric acid, 96% was initially introduced and 83 g of terephthalic acid was introduced. Then, after the system was flushed with nitrogen, 108 g of o-phenylenediamine



was added in portions, which caused the temperature to increase to 97°C. The temperature was then increased to 110°C. 787 g of chlorosulfonic acid was then metered in over the course of 1.5 hours, with the temperature maintained between 110-120°C. After the metered addition, a reaction time of 30 minutes at 110-120°C followed.

The reactor contents were cooled to room temperature, and 1,430 g of water at 5°C were metered in over the course of 1.5 hours. Then, the mixture was after-stirred for an additional 2 hours and then filtered, giving 430 g of moist phenylene-bis-benzimidazole-tetrasulfonic acid.

This press cake was introduced into 4,000 g of water at 40°C and dissolved. Then, 11 g of activated carbon was added. The mixture was stirred for 30 minutes under nitrogen and then filtered. The filtrate was admixed at 50°C with 215 g of sodium chloride and stirred for 2 hours at this temperature. The temperature was reduced to 25°C towards the end of the stirring period, and the mixture was filtered. The resulting product was washed with 1,000 g of 5% by weight sodium chloride solution, giving 488 g of phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt.

The resulting phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt was introduced into 1,610 g of water at 50°C and suspended (pH 2.4). Then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product. Then, 11 g of activated carbon was added; the mixture was heated to 55°C and after-stirred for 2 hours and filtered. The filtrate was treated with 58 g of pure hydrochloric acid. Then, the temperature was maintained at 50°C, and a pH of 3 was adjusted. The mixture was stirred for 2 hours under nitrogen and was cooled to 25°C; the mixture was filtered. The filter cake was then washed with 1,430 g of

water, giving 418 g of purified phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt.

The thus purified phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt was then dried for 10 hours at 140°C and 2 mbar, giving 253 g of end-product.

The thus obtained phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt showed a content of phenylene-bis-benzimidazole-trisulfonic acid disodium salt of about 3.7% by weight. The residual moisture of about 1 - 2 % by weight was not taken into account.

**HR 285: N.H. AP according to the present invention**

609 g of sulfuric acid, 96% was initially introduced, and 83 g of terephthalic acid was introduced. Then, after the system was flushed with nitrogen, 108 g of o-phenylenediamine was added in portions, which caused the temperature to increase to 97°C. The temperature was then increased to 110°C. 787 g of chlorosulfonic acid was then metered in over the course of 1.5 hours, with the temperature maintained between 110-120°C. After the metered addition, the mixture was stirred for a further 10 hours at 110-120°C.

The reactor contents were cooled to room temperature, and 1,430 g of water at 5°C was metered in over the course of 1.5 hours. Then, the mixture was after-stirred for a further 2 hours and then filtered, giving 430 g of moist phenylene-bis-benzimidazole-tetrasulfonic acid.

This press cake was introduced into 4,000 g of water at 40°C and dissolved. Then, 11 g of activated carbon was added. The mixture was stirred for 30 minutes under nitrogen and then filtered. The filtrate was admixed at 50°C with 215 g of sodium chloride and was stirred for 2 hours at this temperature, with the temperature reduced to 25°C towards the

end of the stirring period. Then, the mixture was filtered. The resulting product was washed with 1,000 g of 5% by weight sodium chloride solution, giving 488 g of phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt.

The resulting phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt was introduced into 1,610 g of water at 50°C and suspended (pH 2.4). Then, at 50°C, 60 g of 45% wt. sodium hydroxide solution was added to adjust the pH to 5 and to dissolve the product. Then, 11 g of activated carbon was added, and the mixture was heated to 55°C and after-stirred for 2 hours and filtered. The filtrate was treated with 58 g of pure hydrochloric acid. Then, the temperature was maintained at 50°C, and a pH of 3 was adjusted. The mixture was stirred for 2 hours under nitrogen and cooled to 25°C; the mixture was then filtered. The filter cake was then washed with 1,430 g of water, giving 413 g of purified phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt.

The thus purified phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt was then dried for 10 hours at 140°C and 2 mbar, giving 250 g of end-product.

The thus obtained phenylene-bis-benzimidazole-tetrasulfonic acid disodium salt showed a content of phenylene-bis-benzimidazole-trisulfonic acid disodium salt of about 1.8% by weight. The residual moisture of about 1 - 2 % by weight was not taken into account.

#### CONCLUSION

It is apparent from the above described results of side-by-side comparison experiments and from the attached picture (Attachment A) that the method of the present invention produces a composition that is free of discoloring byproducts (see Attachment A, bottle on the right, showing a white color). In contrast, the method of the prior art produces a

product that is colored (see Attachment A, bottle on the left, showing a pink color).

In my scientific opinion, it is clear that the present invention surprisingly produces a composition that is free of discoloring byproducts. In fact, it has been found that the process of the present invention actually increases the amount of trisulfonic impurities, but that the process surprisingly results in a decrease in discoloration. In contrast, the prior art reduces the amount of the trisulfonic acid impurity, but does not reduce discoloring byproducts.

Further, it is clear that, in this particular process, an extension in reaction time or an increase in reaction temperature leads to an increase in discoloring impurities due to an increase in side reactions, condensations, polymerizations, decompositions, or other subsequent reactions of the product, see HR 144-2. When the extended time and the increased temperature of the present invention were used in conjunction with the process of the prior art, the process of the prior art did not lead to a colorless product. Further, even when the process of the present invention was used in conjunction with the shorter reaction time of the prior art, the resulting product was still discolored. It is apparent that only through the unique process of the present invention that a product free of discoloring impurities can be obtained.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may

jeopardize the validity of this application and of any patent  
issuing thereon.

Date: 14. 11. 2003

Ok

Dr. Oskar Koch